Wound Healing Trajectories in Burn Patients and Their Impact on Mortality

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The rate of wound healing and its effect on mortality has not been well described. The objective of this article is to report wound healing trajectories in burn patients and analyze their effects on in-hospital mortality. The authors used software (WoundFlow) to depict burn wounds, surgical results, and healing progression at multiple time points throughout admission. Data for all patients admitted to the intensive care unit with ≥ 20% TBSA burned were collected retrospectively. The open wound size (OWS), which includes both unhealed burns and unhealed donor sites, was measured. We calculated the rate of wound closure (healing rate), which we defined as the change in OWS/time. We also determined the time delay (DAYS) from day of burn until day on which there was a reduction in OWS < 10%. Data are medians [interquartile range]. There were 38 patients with complete data; 25 had documentation of successful healing (H), and 13 did not (NH). H differed from NH on age (38 years [32–57] vs 63 [51–74]), body mass index (27 [21–28] vs 32 [19–52]), 24-hour fluid resuscitation (12L [10–16] vs 18 [15–20]), pressors during first 48 hours (72% vs 100%), use of renal replacement therapy (32% vs 92%), and mortality (4% vs 100%). Repeated measures analysis of covariance showed a significant difference between survivors and nonsurvivors on OWS as a function of time (*P*<.001). Patients with a positive healing rate (+2%/day) after postburn day 20 had 100% survival whereas those with a negative healing rate (–2%/day) had 100% mortality. For H patients, median DAYS was 41 (28–54); median DAYS/TBSA was 1.3 (1.0–1.9). Survivors had a 0.62% drop in OWS/day, or 4.3%/week. In this cohort of patients with ≥ 20% TBSA, there was a difference in mortality after postburn day 20, between patients with a positive healing rate (+2%/day, 100% survival) and those with a negative healing rate (–2%/day, 100% mortality, *P* < .05). (J Burn Care Res 2014;35:474–479)

The burn wound is the central problem in the care of burn patients. Although patients with extensive thermal injuries epitomize all facets of the multisystem response to injury in a dose-responsive fashion,[1] the taming of this systemic inflammatory response mandates a focus on two things: prevention of burn wound infection and timely burn wound closure. The importance of burn wound infection was highlighted by the marked reduction in postburn mortality occasioned by the introduction of topical mafenide acetate in 1964.[2] The feasibility and the importance of early excision and grafting was appreciated more gradually.[3–7] Few studies have examined the rate of wound healing in burn patients and quantified its

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relationship with mortality. In the absence of such data about our patients, how do we know when we need to enact a new strategy, that is, when is the burn wound not healing at an appropriate rate?

The Lund-Browder chart is a commonly used, paper-based method of estimating the area of burns.[8] We recently developed a computerized version of this chart and validated its accuracy in a manikin study.[9] Development of this tool has made it possible to track healing over time. The purpose of this study was to determine the time course of wound closure in burn patients and analyze the relationship between healing rate and survival. We hypothesized that failure to heal wounds in a timely manner correlates with death. Specifically, we hypothesized that there would be significant differences between survivors and nonsurvivors with respect to velocity of healing. We also hypothesized that at a certain day postburn, survivors and nonsurvivors could be distinguished by the percentage of the body surface area still open.

METHODS

Clinical Setting

The U.S. Army Institute of Surgical Research Burn Center includes a 16-bed burn intensive care unit (BICU) located in a tertiary military teaching hospital. The burn center serves the local civilian and military population needing burn care, as well as all U.S. service members burned during military operations worldwide. Patients (except for 2 military patients) were resuscitated using a clinical decision support system. The system provides crystalloid recommendations every hour based on a target urinary output of 30 to 50 ml/hr. On arrival to the BICU, all intubated, acutely injured patients underwent fiberoptic bronchoscopy and presence or absence of inhalation injury was confirmed by a burn attending. Standard practice for the unit was to perform excision and grafting within 4 days of injury. All patients received the same level of care until deceased or discharged, with no attempts to label any patient as a nonhealer during the study. No attempts were made to use patient's wound healing trajectories to label certain patients as expectant.

Study Design and Participants

After obtaining approval from the U.S. Army Medical Research and Materiel Command Institutional Review Board and ensuring full compliance of the protocol with the U.S. Department of Health and Human Services' Health Insurance Portability and Accountability Act, we conducted a retrospective review of existing WoundFlow data for all patients admitted to the burn center ICU from January 2003 through June 2011 with ≥ 20% TBSA burns. A computerized version of the Lund-Browder chart, WoundFlow,[9] was used during this period of time to track a patient's wound characteristics throughout admission. This software enables users to depict partial and full-thickness burn wounds. Users can also label wounds as donor sites; as burns that have spontaneously healed, that have been excised and grafted, or that have healed after grafting; or as amputated. The software does not readjust the initial TBSA to account for limb loss. However, once an area is labeled as having been amputated, it is no longer considered an open wound. Autografts, and temporary grafts such as allograft or skin substitutes, are differentiated in the software. Wounds are not classified as closed until they have spontaneously healed or have healed after successful definitive surgery. That is, although the placement of allograft, Biobrane, etc. may contribute to wound healing, it does not per se constitute wound healing in this software until final epithelialization has occurred. The software displays the percentage of the body surface area comprising such areas, and saves these data to a database. The majority of patients admitted to the BICU during this period underwent documentation of their wounds in WoundFlow upon admission. WoundFlow diagrams were then updated weekly and after each surgical operation to document the changing status of the wounds. The attending surgeon, surgical resident, and/or wound care nurse were responsible for filling out these diagrams. Only patients who had at least two WoundFlow diagrams, completed (1) on admission and (2) on or after hospital day 14, were included in this study.

We defined open wound size (OWS) as the sum of the TBSA burned, plus the surface area used as donor sites, minus the surface area that had healed. These areas were quantified as percentages of the total surface area. We calculated the normalized OWS = [OWS/TBSA] × 100%. We defined the day of healing as the day on which the OWS was documented as being less than 10%. We determined the time ("DAYS") that elapsed from the day of injury until the day of healing. We calculated the wound healing rate for each patient as the slope of the log-transformed normalized OWS. We divided the patients into two groups: those who healed (H) and those who did not heal (NH) at the time of death or discharge.

Other data collected included age, TBSA, inhalation injury, sex, body mass index (BMI), total 24-hour resuscitation volumes, pressor use in the first 48 hours, and hospital outcomes. All patients were screened for preexisting medical conditions,

including diabetes. Complications such as renal failure (need for continuous renal replacement therapy) and infections (ventilator-associated pneumonia, bacteremia) were recorded. We did not attempt to incorporate associated traumatic injuries into our data collection.

The overwhelming majority of our patients were from the local population with minimal delay in admission from time of burn. Only one patient from each group was a military causality transported into the unit from the combat theater. The transport time from theater to the burn center for both of these patients was 48 hours.

Statistical Analysis

Using SAS version 9.1, continuous variables were compared using the Wilcoxon rank-sum test. Categorical variables were compared using the Chi-square test. Significance was accepted at $P<.05$.

RESULTS

The WoundFlow database contained 82 patients with burns > 20% TBSA. Of these, there were 38 patients who had a sufficient number of diagrams to permit analysis. Of these 38 patients, there were 25 patients who healed (H) and 13 who did not (NH). H differed from NH on age (38 years [32–57] vs 63 years [51–74]), BMI (27 [21–28] vs 32 [19–52]), 24-hour fluid resuscitation (12 L [10–16] vs 18 L [15–20]), pressors during first 48 hours (72% vs 100%), use of renal replacement therapy (32% vs 92%), and mortality (4% vs 100%). There was a nonsignificant trend for NH to have a larger full-thickness burn size. There was no difference between groups in ICU length of stay (LOS), ventilator days, overall hospital LOS, number of surgeries, or time to excision. TBSA, sex, and inhalation injury did not differ between H and NH groups (Table 1). Of the complications evaluated, only the use of continuous renal replacement therapy was significantly different between groups (NH, 12 patients vs H, 8 patients, $P = .04$). There was a nonsignificant trend toward increased prevalence of bacteremia in NH patients. Only one patient in each group had a preexisting diagnosis of diabetes. We were not able to show any other preexisting comorbidities affecting wound failure. Table 2 shows the results of univariate analysis of various predictors of mortality. In this data set, younger age and successful healing were associated with survival.

Figures 1A and B show the raw data for OWS as a function of time, for the H and NH groups separately. Because patients began the hospital stay with different burn sizes, it was helpful to normalize OWS by dividing it by TBSA. This resulted in Figure 2. In this figure, H and NH groups are shown together, along with linear regression of these data for each

Table 1. Comparison of healed and nonhealed patients

Variable	Total (n=38)	NH (n=13)	H (n=25)	*P*
Age (years)	50 (33–63)	63 (51–74)	38 (32–57)	.02
Males	29 (76%)	9 (69%)	20 (80%)	NS
BMI	28 (24–34)	32 (19–52)	27 (21–28)	.03
TBSA	38 (29–54)	40 (32–55)	37 (28–52)	NS
Full	16 (7–29)	22 (8–36)	13 (5–23)	NS
Inhalation injury	18 (47%)	8 (62%)	10 40%)	NS
Twenty-four-hour fluid resuscitation, L	15.1 (10.6–19.2)	17.6 (15.1–20.0)	11.7 (9.5–16.1)	.01
Pressors in first 48 hours	31 (82%)	13 (100%)	18 (72%)	.03
Days till first excision	4 (3–5)	5 (3–6)	4 (3–5)	NS
Number of surgeries	4 (2–7)	5 (2–8)	4 (3–6)	NS
Pneumonia	6 (16%)	1 (8%)	5 (20%)	NS
Bacteremia	25 (66%)	11 (85%)	14 (56%)	.08
CRRT	20 (53%)	12 (92%)	8 (32%)	.004
Days until <10% open wound	N/A	N/A	41 (28–54)	N/A
Days/TBSA	N/A	N/A	1.3 (1.0–1.9)	N/A
ICU LOS, days	36 (22–65)	32 (19–52)	45 (23–69)	NS
Ventilator days	24 (14–50)	27 (19–41)	21 (7–56)	NS
Hospital days	52 (35–77)	32 (19–52)	65 (44–91)	.07
Mortality	14 (37%)	13 (100%)	1 (4%)	<.001

NH = nonhealed, *H* = healed, *TBSA* total body surface area burned, *Full*, full-thickness burn size, *ICU*, intensive care unit, *LOS*, length of stay, *BMI*, body mass index, *VAP*, ventilator-associated pneumonia, *CRRT*, continuous renal replacement therapy; *NS*, not significant; *NA*, not applicable.
Continuous data are presented as medians (interquartile range); categorical data are presented as frequencies (percentages).

Table 2. Mortality data

Variable	Lived (n=24)	Died (n=14)	*P*
Age (years)	38 (32–56)	63 (52–72)	.011
TBSA	38 (31–53)	39 (29–55)	NS
Full	12 (5–23)	19 (9–36)	NS
Sex (male)	19 (79%)	10 (71%)	NS
Inhalation injury	14 (58%)	6 (42%)	NS
Healed	24 (100%)	1 (7%)	< .001

TBSA, total body surface area burned, *Full*, full-thickness burn size; *NS*, not significant; *NA*, not applicable.
Continuous data are presented as medians (interquartile range); categorical data are presented as frequencies (percentages).

of the groups. Clear differences can be seen; r^2 for H = .74; r^2 for NH = .09. Finally, the wound healing rate (slope of the log-transformed normalized OWS) was recalculated and binned for each of three time periods. These data are shown in Figure 3.

The median number of days till healing for the H group (DAYS) was 41 (28–54), and the median DAYS/TBSA for the H group was 1.3.

DISCUSSION

The principal finding in this retrospective study of wound healing rates in burn patients was that survivors and nonsurvivors could be distinguished by their wound healing rates after the 20th postburn day. This suggests that factors that influence wound healing (and early interventions that enhance them) during the first 3 weeks postburn are critical to survival in patients with large burns.

Previously, we had not characterized "wound failure" as a cause of death in burn patients. During a recently conducted a review of autopsies at this burn center, the major categories for cause of death were infections, pulmonary, cardiac, renal, gastrointestinal, multiorgan, and central nervous system.[10] We suspect that wound failure—that is, the presence of large, open wounds, in which multiple attempts at wound closure have been made and failed—played a role in many of these deaths, to include those attributed to infection.

Three factors that most contributed to wound failure stand out in our data (Table 1). Impaired wound healing is a consequence of senescence; thus, the NH group was older.[11] Likewise, obesity is associated with impaired wound healing, and the NH group had a higher BMI.[12] Finally, NH had a larger fluid resuscitation volume; edema contributes to impaired wound healing.[13–16] This represents a potential modifiable target for intervention; further work will be needed before any clinical recommendations can be made with regard to intervention in patients with excessive edema. Although the impact of overresuscitation on abdominal and extremity compartment syndromes has received much attention recently, the possible effect of such "fluid creep" on the success rate of skin grafts has not been discussed as widely.

A previous study described a paper-based version of the analysis we have presented. Weekly Lund-Browder charts were filled out and traced onto a tablet. The open burn wound size was calculated. In contrast to our study, these authors only included the burn wounds in their calculation of the open wound size. They then calculated the rate of change of the open burn wound size and called this the wound closure index. By logistic regression, age, TBSA, and wound closure index were independent predictors of mortality.[17] We believe that the technology we have described here goes beyond the previous report, by making the information on wound healing graphically available at the bedside. Thus, we seek to improve the team's situational awareness about wound healing.

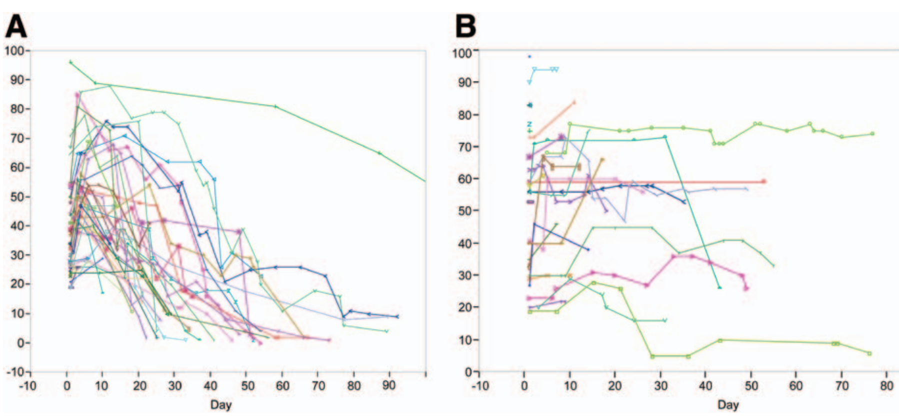

Figure 1. Raw data for open wound size (%) as a function of time. A. For patients who healed (H). B. For patients who did not heal (NH).

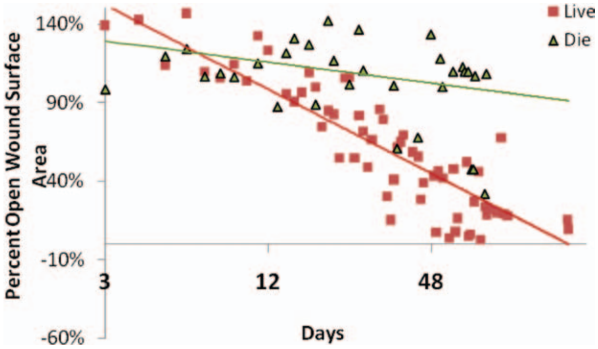

Figure 2. Normalized open wound size (OWS), that is, (OWS/TBSA)×100%, as a function of time. Data for patients who healed (H) are depicted as squares. Data for patients who did not heal (NH) are depicted as triangles. Lines are fitted by linear regression to the H and NH data separately.

However, we have not yet documented the clinical impact of such improved awareness.

This study is limited by its small size and retrospective nature. A large number of eligible patients did not have the required number of wound mappings completed to be considered in our review, which contributed to our small sample size. The system itself is not difficult to use, with most operators reaching proficiency in very little time. However, some training is required. This reduces the usability of the system by rotating residents. Hence, we shifted responsibility from rotating residents to wound care nurses, with an increase in compliance. Inhalation injury was a dichotomous variable and was not graded based on severity. It is possible we may have detected a relationship between severe inhalation injury and wound healing rates. As described in previous works, the tendency of the Lund-Browder chart to underestimate the contributions of the trunk to TBSA is magnified as BMI increases, which makes it difficult to analyze obesity's true effect on wound healing trajectories.[18] Taking body habitus into account is a possible future modification of WoundFlow. This study likely features selection bias; patients with problematic wounds may have been more likely to undergo heightened scrutiny and more frequent use of the WoundFlow software. Finally, the purpose of this study was to underscore the importance of successful wound closure to ultimate survival in patients with major burns. We do not intend to use these results of this preliminary study to consign patients, who may have been inadequately treated initially, to an expectant (terminally ill) category based on their wound status at day 20.

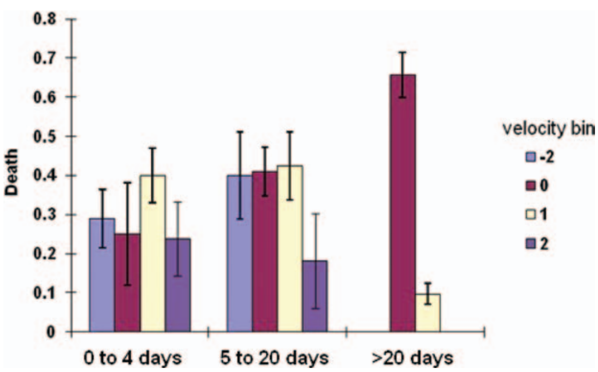

Figure 3. Relationship of wound healing rate ("velocity") to likelihood of death. For each of three time periods, the velocity was recalculated and sorted into four groups, or bins (–2, 0, 1, and 2). By day 20, patients appeared to recategorize themselves into only two remaining groups: those with a positive velocity of 1, whose likelihood of death was low; and those with a velocity of 0, whose likelihood of death was very high. These two groups were statistically different on risk of death.

CONCLUSIONS

In this cohort of patients with ≥20% TBSA burns, there was a difference in mortality by postburn day 20 between patients with a positive healing rate (+2%/day, 100% survival) and those with a negative healing rate (–2%/day, 100% mortality, $P < .05$). Patients who eventually healed to less than 10% OWS, had on average a 0.62% drop in OWS/day, or 4.3%/week. Increased age, increased BMI, and larger fluid resuscitation volumes were associated with decreased wound healing trajectories.

In conclusion, the late Dr. John F. Burke succinctly summarized the burn care problem as follows: "excise the dead, close the wound, and maintain the normal" (JF Burke, personal communication, 2000). With the present study we have aimed to quantify this process.

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This study was conducted under a protocol reviewed and approved by the US Army Medical Research and Materiel Command Institutional Review Board and was fully compliant with the US Department of Health and Human Services' HIPAA.

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